WEST Search History

DATE: Thursday, December 12, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L1	mucociliary clearance and (kunitz or bikunin or aprotinin)	9	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 9 of 9 returned.

1. Document ID: US 20020086020 A1

L1: Entry 1 of 9 File: PGPB Jul 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020086020
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020086020 A1

TITLE: Method for improving the half-life of soluble viral receptors on mucosal membranes

PUBLICATION-DATE: July 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lee, Peter P.	Menlo Park	CA	US	

US-CL-CURRENT: 424/147.1; 424/133.1, 424/134.1, 424/135.1, 424/136.1, 424/141.1, 424/148.1, 424/149.1, 424/150.1, 424/159.1, 424/160.1, 424/161.1, 424/164.1, 424/165.1, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

2. Document ID: US 20020010318 A1

L1: Entry 2 of 9 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020010318
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020010318 A1

TITLE: Secretory leukocyte protease inhibitor dry powder pharmaceutical compositions

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Niven, Ralph W.	Redwood City	CA	US	
Wright, Clifford D.	Boulder	CO	US	
Chang, Byeong S.	Thousand Oaks	CA	US	

US-CL-CURRENT: 530/350; 435/183

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

3. Document ID: US 20010006939 A1

L1: Entry 3 of 9 File: PGPB Jul 5, 2001

PGPUB-DOCUMENT-NUMBER: 20010006939
PGPUB-FILING-TYPE: new-utility
DOCUMENT-IDENTIFIER: US 20010006939 A1

'TITLE: SECRETORY LEUKOCYTE PROTEASE INHIBITOR DRY POWDER PHARMACEUTICAL COMPOSITIONS

PUBLICATION-DATE: July 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
NIVEN, RALPH W.	REDWOOD CITY	CA	US	
WRIGHT, CLIFFORD D.	BOULDER	CO	US	
CHANG, BYEONG S.	THOUSAND OAKS	CA	US	

US-CL-CURRENT: 514/2; 435/69.1, 514/44

☐ 4. Document ID: US 6365156 B1

L1: Entry 4 of 9 File: USPT Apr 2, 2002

US-PAT-NO: 6365156
DOCUMENT-IDENTIFIER: US 6365156 B1

TITLE: Method for improving the half-life of soluble viral-specific ligands on mucosal membranes

DATE-ISSUED: April 2, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lee; Peter P.	Palo Alto	CA		

US-CL-CURRENT: 424/147.1; 424/159.1, 424/163.1, 424/164.1, 424/196.11

ABSTRACT:

This invention relates to methods of increasing the half-life of a viral-specific ligand on a mucosal membrane by modifying the viral-specific ligand to bind the bacteria colonized on the mucosal membrane. The invention also provides a chimeric molecule comprising a viral-specific ligand and a bacterial-specific ligand.

19 Claims, 2 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

☐ 5. Document ID: US 5693608 A

L1: Entry 5 of 9 File: USPT Dec 2, 1997

US-PAT-NO: 5693608
DOCUMENT-IDENTIFIER: US 5693608 A

TITLE: Method of administering a biologically active substance

DATE-ISSUED: December 2, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bechgaard; Erik	Hellerup			DK
Gizurarson; Sveinbjorn	Keflavik			IS
Hjortkj.ae butted.r; Rolf Kuhlman	Humleb.ae butted.r			DK

US-CL-CURRENT: 514/2; 514/4, 530/300

ABSTRACT:

A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.l to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.l of an n-ethylene glycol containing vehicle including at least one n-ethylene glycol represented by the formula:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

30 Claims, 16 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 16

☐ 6. Document ID: US 5534496 A

L1: Entry 6 of 9 File: USPT Jul 9, 1996

US-PAT-NO: 5534496
DOCUMENT-IDENTIFIER: US 5534496 A

TITLE: Methods and compositions to enhance epithelial drug transport

DATE-ISSUED: July 9, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lee; Vincent H.	Monterey Park	CA		
Yen; Wan-Ching	Columbus	OH		

US-CL-CURRENT: 514/17; 424/434, 514/18, 514/19, 530/330, 530/331

ABSTRACT:

Methods and compositions provided for enhancing the transport of drugs (including peptides, oligonucleotides, proteins and conventional drugs) across epithelial cells at mucosal sites. The methods and compositions include the use of a peptide comprising at least two amino acids, such as Pro-Leu-Gly-Pro-Arg or Pro-Leu, and a protective group such as phenylazo-benzyloxycarbonyl, N-methyl, t-butyloxycarbonyl, fluoroenylmethyloxycarbonyl or carbobenzoxy, at the N-terminus, or in a mixture of such peptides in a sufficient amount to enhance the drug transport across epithelial cells at mucosal sites. Preferably, the peptide comprises 2 to 5 amino acids; the N-terminal amino acids are preferably Pro-Leu. The peptide with the drug are introduced to the mucosal site in a physical mixture, a conjugated form or by a microcapsule, microsphere, liposome, cell, bacteria, virus or food vesicle carrier by an oral, nasal, pulmonary, buccal, rectal, transdermal, vaginal or ocular route.

8 Claims, 37 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 11

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 7. Document ID: US 5428006 A

L1: Entry 7 of 9 File: USPT Jun 27, 1995

US-PAT-NO: 5428006
DOCUMENT-IDENTIFIER: US 5428006 A

TITLE: Method of administering a biologically active substance

DATE-ISSUED: June 27, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bechgaard; Erik	Hellerup			DK
Gizurarson; Sveinbjorn	Keflavik			IS
Hjortkjaer; Rolf K.	Humlebaer			DK

US-CL-CURRENT: 514/3; 514/2, 514/4, 530/303, 530/307, 530/311, 530/313

ABSTRACT:

A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.1 to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.1 of a n-glycofurol-containing vehicle including at least one n-glycofurol represented by the formula: ##STR1## wherein n is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

22 Claims, 12 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 8. Document ID: US 5397771 A

L1: Entry 8 of 9 File: USPT Mar 14, 1995

US-PAT-NO: 5397771
DOCUMENT-IDENTIFIER: US 5397771 A

TITLE: Pharmaceutical preparation

DATE-ISSUED: March 14, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bechgaard; Erik	Hellerup			DK
Gizurarson; Sveinbjorn	Keflavik			IS
Hjortkjaer; Rolf K.	Humlebaer			DK

US-CL-CURRENT: 514/2; 514/3, 514/4, 530/303, 530/307, 530/311, 530/313

'ABSTRACT:

A pharmaceutical preparation for application of an effective amount of one or more biologically active substance(s) to a mucosal membrane of a mammal comprising an n-glycofurol represented by the formula I: ##STR1## wherein n is 1 to 4 in an amount from: 0.1-30% preferably 0.1-20% most preferably 1-15% in water, or in vegetable oil or n-ethylene glycol(s) represented by formula II:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is 2 to 8, or in a mixture thereof. Nasal administration of the preparation produces a high plasma concentration of the pharmaceutically active substance(s) nearly as rapid as by i.v. administration.

29 Claims, 16 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 16

☐ 9. Document ID: JP 2002532558 W WO 200037099 A2 AU 200019878 A EP 1140150 A2 CN 1334743 A

L1: Entry 9 of 9 File: DWPI Oct 2, 2002

DERWENT-ACC-NO: 2000-452127
DERWENT-WEEK: 200279

TITLE: Stimulating mucociliary clearance rate of mucus and sputum in lung airways for treating lung diseases such as cystic fibrosis and bronchitis involves administering a Kunitz-type serine protease inhibitor

INVENTOR: HALL, R; NEWTON, B B ; POLL, C T ; TAYLOR, W J A

PRIORITY-DATA: 1999US-0441966 (November 17, 1999), 1998US-0218913 (December 22, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2002532558 W	October 2, 2002		227	A61K038/55
WO 200037099 A2	June 29, 2000	E	173	A61K038/57
AU 200019878 A	July 12, 2000		000	A61K038/57
EP 1140150 A2	October 10, 2001	E	000	A61K038/57
CN 1334743 A	February 6, 2002		000	A61K038/57

INT-CL (IPC): A61 K 9/12; A61 K 9/72; A61 K 38/55; A61 K 38/57; A61 K 47/02; A61 P 11/00; A61 P 11/02; A61 P 11/06; A61 P 11/12; A61 P 27/16; A61 P 43/00; C07 K 14/81

ABSTRACTED-PUB-NO: WO 200037099A
BASIC-ABSTRACT:

NOVELTY - Accelerating the rate of mucociliary clearance in a subject comprising administering a composition (I) comprising a Kunitz-type serine protease inhibitor (KSPI).

ACTIVITY - Antiinflammatory. The effect of the Kunitz family serine protease inhibitor, bikunin, was studied on sheep tracheal mucus velocity (TMV) over 8 hours after treatment with bikunin. 9 mg bikunin (3 ml of 3 mg/ml) was administrated by a nebulized aerosol to the airways and to measure TMV, 5-10 radiopaque Teflon (RTM) particles were insufflated into the trachea via a catheter placed within the endotracheal tube. The movement of the Teflon (RTM) particles was then measured for 1 minute. TMV was calculated from the average distance in a cephalad direction traveled per minute for 5 - 10 Teflon particles. Baseline TMV was measured immediately prior to administration of the aerosol for 8 hours with an interval of 1 hour. The results showed that bikunin aerosol delivered to sheep airways significantly increased TMV at 8 hours compared to the same time for a group of animals receiving phosphate buffered saline (PBS) vehicle aerosol.

*MECHANISM OF ACTION - Serine protease inhibitor.

USE - Kunitz-type serine protease inhibitors are useful for stimulating the rate of mucociliary clearance of mucus and sputum in the lung airways (claimed). The inhibitors are useful for treating lung diseases such as cystic fibrosis, chronic bronchitis, bronchiectasis and chronic sinusitis and glue ear caused by retention and accumulation of mucus.

ADVANTAGE - The composition reduces or eliminates mucus and sputum in lung airways in patients with chronic obstructive lung disease and reduces the risk of secondary lung infections and other adverse side effects, as well as avoiding or delaying the need for lung transplant surgery in cystic fibrosis patients. Inhibitors are human proteins and therefore reduce the risk of kidney damage on administration of large doses of Trasylol proteins.

Terms	Documents
mucociliary clearance and (kunitz or bikunin or aprotinin)	9

```
=> file .nash
=> s mucociliary clearance and kunitz
L1            0 FILE MEDLINE
L2            1 FILE CAPLUS
L3            1 FILE SCISEARCH
L4            0 FILE LIFESCI
L5            0 FILE BIOSIS
L6            0 FILE EMBASE

TOTAL FOR ALL FILES
L7            2 MUCOCILIARY CLEARANCE AND KUNITZ

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8             2 DUP REM L7 (0 DUPLICATES REMOVED)

=> d ibib abs

L8   ANSWER 1 OF 2  SCISEARCH  COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER:    2001:513776  SCISEARCH
THE GENUINE ARTICLE: 447AR
TITLE:               Na+ transport in normal and CF human bronchial epithelial
                     cells is inhibited by BAY 39-9437
AUTHOR:              Bridges R J (Reprint); Newton B B; Pilewski J M; Devor D
                     C; Poll C T; Hall R L
CORPORATE SOURCE:    Univ Pittsburgh, Dept Cell Biol & Physiol, 3500 Terrace
                     St, S310 Biomed Sci Tower, Pittsburgh, PA 15261 USA
                     (Reprint); Univ Pittsburgh, Dept Cell Biol & Physiol,
                     Pittsburgh, PA 15261 USA; Bayer Pharmaceut Div, Slough SL2
                     4LY, Berks, England
COUNTRY OF AUTHOR:   USA; England
SOURCE:              AMERICAN JOURNAL OF PHYSIOLOGY-LUNG CELLULAR AND MOLECULAR
                     PHYSIOLOGY, (JUL 2001) Vol. 281, No. 1, pp. L16-L23.
                     Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE,
                     BETHESDA, MD 20814 USA.
                     ISSN: 1040-0605.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     33
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       To test the hypothesis that Na+ transport in human bronchial epithelial
     (HBE) cells is regulated by a protease-mediated mechanism, we investigated
     the effects of BAY 39-9437, a recombinant Kunitz-type serine
     protease inhibitor, on amiloride-sensitive short-circuit current of normal
     [non-cystic fibrosis (CF) cells] and CF HBE cells. Mucosal treatment of
     non-CF and CF HBE cells with BAY 39-9437 decreased the short-circuit
     current, with a half-life of similar to 45 min. At 90 min, BAY 39-9437
     (470 nM) reduced Na+ transport by similar to 70%. The inhibitory effect of
     BAY 39-9437 was concentration dependent, with a half-maximal inhibitory
     concentration of similar to 25 nM. Nai transport was restored to control
     levels, with a half-life of similar to 15 min, on washout of BAY 39-9437.
     In addition, trypsin (1 muM) rapidly reversed the inhibitory effect of BAY
     39-9437. These data indicate that Na+ transport in HBE cells is activated
     by a BAY 39-9437-inhibitable, endogenously expressed serine protease. BAY
     39-9437 inhibition of this serine protease maybe of therapeutic potential
     for the treatment of Na+ hyperabsorption in CF.


=> d ibib abs 2

L8   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2000:441647  CAPLUS
DOCUMENT NUMBER:         133:84295
TITLE:                   Kunitz-type serine proteinase inhibitors for
                         accelerating the rate of mucociliary
                         clearance
INVENTOR(S):             Hall, Roderick; Poll, Christopher T.; Newton, Benjamin
                         B.; Taylor, William J. A.
PATENT ASSIGNEE(S):      Bayer Aktiengesellschaft, Germany
```

SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037099	A2	20000629	WO 1999-GB4381	19991222
WO 2000037099	A3	20001026		

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1140150	A2	20011010	EP 1999-963636	19991222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002532558	T2	20021002	JP 2000-589209	19991222

PRIORITY APPLN. INFO.:
US 1998-218913 A 19981222
US 1999-441966 A 19991117
WO 1999-GB4381 W 19991222

AB The instant invention provides for a compn. and method for using **Kunitz**-type serine protease inhibitors, e.g., aprotinin or bikunin, for stimulating the rate of **mucociliary clearance** of mucus and sputum in lung airways of subjects afflicted with mucociliary dysfunctions such as cystic fibrosis.

=> s mucociliary clearance and bikunin
TOTAL FOR ALL FILES
L15 1 MUCOCILIARY CLEARANCE AND BIKUNIN

=> d ibib abs

L15 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:441647 CAPLUS
DOCUMENT NUMBER: 133:84295
TITLE: Kunitz-type serine proteinase inhibitors for accelerating the rate of **mucociliary clearance**
INVENTOR(S): Hall, Roderick; Poll, Christopher T.; Newton, Benjamin B.; Taylor, William J. A.
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037099	A2	20000629	WO 1999-GB4381	19991222
WO 2000037099	A3	20001026		

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1140150	A2	20011010	EP 1999-963636	19991222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, SI, LT, LV, FI, RO
JP 2002532558 T2 20021002 JP 2000-589209 19991222
PRIORITY APPLN. INFO.: US 1998-218913 A 19981222
US 1999-441966 A 19991117
WO 1999-GB4381 W 19991222

AB The instant invention provides for a compn. and method for using Kunitz-type serine protease inhibitors, e.g., aprotinin or **bikunin**, for stimulating the rate of **mucociliary clearance** of mucus and sputum in lung airways of subjects afflicted with mucociliary dysfunctions such as cystic fibrosis.

=> s bikunin
TOTAL FOR ALL FILES
L22 872 BIKUNIN

=> l22 and (poteinase inhibitor or protease inhibitor)
L22 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l22 and (poteinase inhibitor or protease inhibitor)
TOTAL FOR ALL FILES
L29 213 L22 AND (POTEINASE INHIBITOR OR PROTEASE INHIBITOR)

=> s l22 and sodium
TOTAL FOR ALL FILES
L36 56 L22 AND SODIUM

=> s l36 and l29
TOTAL FOR ALL FILES
L43 8 L36 AND L29

=> s l43 not 2000-2002/py
TOTAL FOR ALL FILES
L50 3 L43 NOT 2000-2002/PY

=> dup rem l50
PROCESSING COMPLETED FOR L50
L51 2 DUP REM L50 (1 DUPLICATE REMOVED)

=> d ibib abs

L51 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:290844 BIOSIS
DOCUMENT NUMBER: PREV199799590047
TITLE: Human pre-alpha-inhibitor: Isolation from a by-product of industrial scale plasma fractionation and structural analysis of its H3 heavy chain.
AUTHOR(S): Mizon, Charlotte; Heron, Antoine; Capon, Callioppe; Sautiere, Pierre; Michalski, Catherine; Sesboue, Richard; Mizon, Jacques (1)
CORPORATE SOURCE: (1) Lab. Biochimie, Fac. Pharmacie, Ave. du Professeur Laguesse, B.P. 83, F-59006 Lille France
SOURCE: Journal of Chromatography B, (1997) Vol. 692, No. 2, pp. 281-291.
ISSN: 0378-4347.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Pre-alpha-inhibitor (P-alpha-I) is a serine proteinase inhibitor from human plasma. It comprises **bikunin** (BK) responsible for antiprotease activity, covalently linked to a heavy chain H3. Here we describe its isolation from a side fraction of an industrial preparation of plasma clotting factors. By using a highly specific polyclonal antiserum prepared from rabbit immunized with a H3P polypeptide obtained in a bacterial expression system, we were able to identify the fractions containing P-alpha-I. Then, taking advantage of the differential affinity of the members of the inter-alpha-inhibitor family (I-alpha-I) for heparin-Sepharose and blue-Sepharose, we isolated P-alpha-I. Its specific antitryptic activity was 580 IU/g, higher than that of I-alpha-I: 420

IU/g. Its M-r, determined by **sodium** dodecyl sulfate polyacrylamide gel electrophoresis, with or without prior reduction, was 130 000. Its peptide chains were identified by N-terminal sequencing. The H3 heavy chain was isolated from P-alpha-I by alkaline dissociation and anion-exchange chromatography. Its electrophoretic mobility was compared to that of the H1 and H2 heavy chains of I-alpha-I. In reducing conditions, it was quite similar to that of H2 (M-r 85 000) but clearly different from that of H1 (M-r 78 000). Thus, the so-determined apparent M-r of H3 was overestimated since its molecular mass determined by MALDI-TOF was 74 100. This result agrees with the proposed structure for H3. Indeed, by carbohydrate analysis and PNGase F digestion, we demonstrate that the two potential N-glycosylation sites present in the core-protein (theoretical mass: 69 454) are really occupied by two N-glycans, probably of biantennary type.

=> d ibib abs 2

L51 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97018241 MEDLINE
DOCUMENT NUMBER: 97018241 PubMed ID: 8864857
TITLE: Inter-alpha-trypsin inhibitor and its related proteins in Syrian hamster urine and plasma.
AUTHOR: Yamamoto T; Yamamoto K; Sinohara H
CORPORATE SOURCE: Department of Biochemistry, Kinki University School of Medicine, Osaka.
SOURCE: JOURNAL OF BIOCHEMISTRY, (1996 Jul) 120 (1) 145-52. Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970114

AB Urinary excretion of trypsin inhibitor increased after injection of a carcinogen, N-nitrosobis(2-oxopropyl)amine, into Syrian hamsters. Two inhibitors were purified to apparent homogeneity from urine collected during the course of the carcinogenesis experiment. Their complete amino acid sequences were determined by Edman degradation of the intact proteins and partially degraded fragments. One corresponded to a hamster liver cDNA clone that hybridized with human **bikunin** probe [Ide et al, (1994) Biochim, Biophys. Acta 1209, 286-292], except that the protein sequence lacked C-terminal serine and the other was trypstatin, the C-terminal half of the **bikunin** molecule. Three proteins containing covalently linked **bikunin** were also identified in pooled blood plasma. They were all dissociated into heavy and light chains by treatment with chondroitinase ABC or 50 mM NaOH, but not by heating at 100 degrees C in the presence of **sodium** dodecyl sulfate and dithiothreitol, N-terminal amino acid sequence analyses of the native chains and partially degraded fragments thereof revealed that these proteins are (i) human-type inter-alpha-trypsin inhibitor, consisting of heavy chains 1 and 2 and **bikunin**, (ii) bovine-type inter-alpha-trypsin inhibitor, consisting of heavy chains 2 and 3 and **bikunin**, and (iii) pre-alpha-trypsin inhibitor, consisting of heavy chain 3 and **bikunin**. Heterodimer of **bikunin** /heavy chain 1 or **bikunin**/heavy chain 2 was not detected. These results suggest that the composition, and hence function, of the inter-alpha-trypsin inhibitor family differs considerably from species to species.

=> s l36 not 2000-2002/py
TOTAL FOR ALL FILES
L58 37 L36 NOT 2000-2002/PY

=> dup rem l57
PROCESSING COMPLETED FOR L57
L59 9 DUP REM L57 (0 DUPLICATES REMOVED)

=> d ibib abs 1-9

L59 ANSWER 1 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999399055 EMBASE
TITLE: Proteoglycan core protein in human urine and its possible role on calcium oxalate urolithiasis.
AUTHOR: Yoshimura K.; Miyake O.; Tsujihata M.; Yoshioka T.; Yamaguchi S.; Koide T.; Takahara S.; Okuyama A.
CORPORATE SOURCE: Dr. K. Yoshimura, Department of Urology, Osaka University Medical School, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan. ky135@uro.med.osaka-u.ac.jp
SOURCE: International Journal of Urology, (1999) 6/11 (567-571).
Refs: 26
ISSN: 0919-8172 CODEN: IJURF3
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: There are only a few papers reporting on the role of proteoglycan core protein in calcium oxalate stone formation. The present study was carried out to investigate the role of core protein of proteoglycan in human urine on calcium oxalate (CaOx) crystallization. Methods: Proteoglycans were collected from whole human urine. The covalently bound glycosaminoglycans (GAG) of proteoglycans were then digested by GAG lyase. The inhibitory activity on CaOx crystal growth in vitro was measured before and after enzyme digestion of proteoglycans. **Sodium** dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) of the core protein of proteoglycans and the analysis of amino acid sequence were performed. Results: The core protein showed significant inhibitory activity on CaOx crystal growth, which scarcely changed when compared with that of proteoglycans before enzyme digestion. The SDS-PAGE revealed that the core protein was a single unit with a molecular weight of 26 kDa and amino acid sequencing demonstrated high homology to interalpha-trypsin inhibitor (ITI) light chain (**bikunin**) with Kunitz inhibitor domain as a core protein. Conclusions: The results suggested that human urine contains proteoglycans and a major part of them is ITI light chain (**bikunin**). The Kunitz inhibitor domain, a core protein of **bikunin**, has significant inhibitory activity on CaOx crystallization without GAG bound covalently to the core protein.

L59 ANSWER 2 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999370183 EMBASE
TITLE: Role of urinary **bikunin** in the inhibition of calcium oxalate crystallization.
AUTHOR: Atmani F.; Khan S.R.
CORPORATE SOURCE: Dr. S.R. Khan, University of Florida, College of Medicine, Department of Pathology, Gainesville, FL 32610, United States. khan@ufl.edu
SOURCE: Journal of the American Society of Nephrology, (1999) 10/SUPPL. 14 (S385-S388).
Refs: 20
ISSN: 1046-6673 CODEN: JASNEU
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Several urinary macromolecules are known to modulate calcium oxalate (CaOx) crystallization. One of these is urinary **bikunin**, the light chain of inter-.alpha.-inhibitor. **Bikunin** has been demonstrated to be an efficient inhibitor of CaOx crystal growth; however, its inhibitory activity against other events in CaOx crystallization has not been fully investigated. To assess the potential of urinary **bikunin** as an effective inhibitor, its effects on CaOx crystal nucleation and aggregation were evaluated. Nucleation and aggregation of CaOx crystals were studied by measuring turbidity at 620 nm. In the nucleation assay, crystallization was induced by mixing calcium chloride and **sodium** oxalate, at final concentrations of 3 and 0.5 mM,

respectively. Both solutions were buffered with 0.05 M Tris, 0.15 M NaCl, pH 6.5. Nucleation measurements were performed at 37.degree.C, with stirring at 800 rpm. Inhibition of nucleation was estimated by comparing the induction time in the presence of the inhibitor with control values. In the aggregation assay, the optical density of the solution containing CaOx monohydrate crystals was monitored. Inhibition of aggregation was evaluated by comparing the turbidity slope in the presence of the inhibitor with control values. The data showed that urinary **bikunin**, at concentrations of 2.5 to 20 .mu.g/ml, retarded crystal nucleation by 67 to 58% and inhibited crystal aggregation by 59 to 80%. According to these results, it seems that urinary **bikunin** is an efficient inhibitor of crystal nucleation and aggregation. Its presence in the kidneys and urine may protect subjects against CaOx crystallization and kidney stone formation.

L59 ANSWER 3 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999091047 EMBASE
TITLE: Differential expression of urinary inter-.alpha.-trypsin inhibitor trimers and dimers in normal compared to active calcium oxalate stone forming men.
AUTHOR: Marengo S.R.; Resnick M.I.; Yang L.; Chung J.-Y.
CORPORATE SOURCE: S.R. Marengo, Urology Research Laboratories, School of Medicine, 2109 Adelbert Rd., Cleveland, OH 44106, United States
SOURCE: Journal of Urology, (1998) 159/5 (1444-1450).
Refs: 24
ISSN: 0022-5347 CODEN: JOURAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Purpose: We determine if the immunoreactive profile of urinary inter-.alpha.-trypsin inhibitor can be used to distinguish between normal individuals and individuals with calcium oxalate stone disease. Materials and Methods: Urinary proteins were dialyzed against water (15 kDa. molecular weight cutoff), lyophilized and resolved by **sodium** dodecyl sulfate-polyacrylamide gel electrophoresis (6% acrylamide, reducing conditions) followed by Western blot. Inter-.alpha.-trypsin immunoreactive proteins were detected by enhanced chemiluminescence. Stone formation was confirmed to be active radiologically or passed as stone or gravel within 12 months of the sample. Stone composition was confirmed crystallographically. Normal individuals had no personal or familial history of urolithiasis and matched stone forming patients regarding race (white) and age (23 to 71 years old). Urine from a total of 101 individuals was analyzed. Results: The intact inter-.alpha.-trypsin trimer (.apprx.220 to 240 kDa.) and heavy chain (HC) 2-**bikunin**/HC1-**bikunin** dimers (.apprx.115 to 130 kDa.) were detected more often in stone forming men (23 of 26 [89%] and 26 of 26 [100%], respectively) than in normal individuals (6 of 26 [23%] and 5 of 26 [19%], respectively, $p < 0.0001$). In those normal individuals who expressed inter-.alpha.-trypsin trimer and HC-**bikunins** the relative intensities were 5.3 .+-. 1.4% and 16.3 .+-. 17.1% of the stone forming controls, respectively. The identity of high molecular weight-inter-.alpha.- trypsin immunoreactive bands was confirmed using antibodies against the individual subunits (HC1, HC2, HC3, **bikunin**). In contrast to men high molecular weight-inter-.alpha.-trypsin's were readily detected in normal and stone forming women with equal frequency (inter-.alpha.-trypsin-trimer $p = 0.1337$, HC- **bikunins** $p = 0.2836$): inter-.alpha.-trypsin-trimer 17 of 18 [94%] and 9 of 13 [77%]; HC-**bikunins** 17 of 18 [94%] and 10 of 13 [85%]). Inter-.alpha.-trypsin- trimer and HC-**bikunins**, respectively, were detected in 2 and 5 of 10 patients with chronic renal disease. Expression was not related to hematuria or proteinuria. Conclusions: Immunoreactive profiles of urinary proteins may be able to be developed into a useful diagnostic tool to identify active stone formation, although a separate panel may be required for men and women. It is possible that these differences may provide clues as to why the incidence of stone disease is higher in men than women.

L59 ANSWER 4 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998343313 EMBASE
TITLE: **Bikunin** present in human peritoneal fluid is in part derived from the interaction of serum with peritoneal mesothelial cells.
AUTHOR: Thomas G.J.; Yung S.; Davies M.
CORPORATE SOURCE: Dr. M. Davies, Institute of Nephrology, Royal Infirmary, Cardiff CF2 1SZ, Wales, United Kingdom. daviesm6@cf.ac.uk
SOURCE: American Journal of Pathology, (1998) 153/4 (1267-1276).
Refs: 57
ISSN: 0002-9440 CODEN: AJPAA4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We recently reported that peritoneal fluid mainly contains two proteoglycans; one is the interstitial proteoglycan referred to as decorin, and the other an uncharacterized small chondroitin sulfate proteoglycan. In the present study, we have used a two-step process to isolate the small chondroitin sulfate proteoglycan free of decorin. The purified molecule ran as a single band on **sodium** dodecyl sulfate-polyacrylamide gel electrophoresis with apparent molecular mass 50 kd made up of a chondroitin-4-sulfate glycosaminoglycan chain and a 30-kd core protein. NH2-terminal analysis of the core protein showed significant sequence homology with **bikunin**, a component of the human inter-.alpha.-trypsin inhibitor (I.alpha.I) family. A Western blot analysis using anti-human inter-.alpha.-trypsin inhibitor confirmed the identity of the small chondroitin sulfate proteoglycan as **bikunin** , and a trypsin inhibitor counterstain assay confirmed its anti-trypsin activity. Examination of serum from patients receiving continuous peritoneal dialysis suggests that free **bikunin** in peritoneal fluid may be the result of leakage of serum proteins into the peritoneum. Our findings further show that the interaction of serum with peritoneal mesothelial cells offers a new and novel explanation for the presence of **bikunin** in peritoneal fluid.

L59 ANSWER 5 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998229876 EMBASE
TITLE: Inter-.alpha.-inhibitor in urine and calcium oxalate urinary crystals.
AUTHOR: Dawson C.J.; Grover P.K.; Ryall R.L.
CORPORATE SOURCE: Prof. R.L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, SA 5042, Australia
SOURCE: British Journal of Urology, (1998) 81/1 (20-26).
Refs: 28
ISSN: 0007-1331 CODEN: BJURAN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective. To determine which chains of inter-.alpha.-inhibitor (I.alpha.I) are present in urine and whether they are also round in calcium oxalate (CaOx) crystals generated in human urine. Materials and methods. Fresh urine specimens were collected from five women and five men with no previous history of stone disease. An aliquot of each urine was retained for analysis, the remainder treated with a standard load of oxalate and the CaOx crystals precipitated from each specimen demineralized with ethylenediamine tetracetic acid. The resulting organic extracts from crystals and their corresponding urine samples were subjected to **sodium** dodecyl sulphate gel electrophoresis analysis and Western blotting using a commercial polyclonal antibody to I.alpha.I. Results. Heavy chain 1 (H1) and 2 (H2) of I.alpha.I were commonly found in every urine sample, and in the CaOx crystals precipitated from those urine samples. Several protein bands were visible in urine samples from both sexes in the molecular mass range 25-70 kDa, which may be **bikunin** or its fragments. As well as H1 and H2, the crystals from both sexes contained a protein band at .simeq. 33 kDa. In many cases there appeared to be no direct relationship between the

proteins detected in the crystals and the urine samples from which they were derived, which probably reflects the well known instability of I.alpha.I and the occurrence of a range of **bikunin** fragments in urine. Conclusion. These results show for the first time that H1 and H2, are present in human urine and urinary CaOx crystals, that the **bikunin** chain of I.alpha.I is not the only part of the molecule capable of participating in CaOx crystallization in urine, and in theory at least, in the regulation of crystallization events in stone formation. It is also apparent that significant fragmentation of I.alpha.I occurs both in vivo and in vitro, and this must be considered in any study attempting to elucidate the influence of this protein in the formation of CaOx stones.

L59 ANSWER 6 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97155611 EMBASE
DOCUMENT NUMBER: 1997155611
TITLE: Human pre-.alpha.-inhibitor: Isolation from a by-product of industrial scale plasma fractionation and structural analysis of its H3 heavy chain.
AUTHOR: Mizon C.; Heron A.; Capon C.; Sautiere P.; Michalski C.; Sesboue R.; Mizon J.
CORPORATE SOURCE: J. Mizon, Lab. Biochimie (DRED EA 1052), Faculte de Pharmacie, Avenue du Professeur Laguesse, F-59006 Lille, France
SOURCE: Journal of Chromatography B: Biomedical Applications, (1997) 692/2 (281-291).
Refs: 23
ISSN: 0378-4347 CODEN: JCBBEP
PUBLISHER IDENT.: S 0378-4347(97)00012-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Pre-.alpha.-inhibitor (P.alpha.I) is a serine proteinase inhibitor from human plasma. It comprises **bikunin** (BK) responsible for antiprotease activity, covalently linked to a heavy chain H3. Here we describe its isolation from a side fraction of an industrial preparation of plasma clotting factors. By using a highly specific polyclonal antiserum prepared from rabbit immunized with a H3P polypeptide obtained in a bacterial expression system, we were able to identify the fractions containing P.alpha.I. Then, taking advantage of the differential affinity of the members of the inter-a-inhibitor family (I.alpha.I) for heparin-Sepharose and blue-Sepharose, we isolated P.alpha.I. Its specific antitryptic activity was 580 IU/g, higher than that of I.alpha.I: 420 IU/g. Its M(r), determined by **sodium** dodecyl sulfate polyacrylamide gel electrophoresis, with or without prior reduction, was 130 000. Its peptide chains were identified by N-terminal sequencing. The H3 heavy chain was isolated from P.alpha.I by alkaline dissociation and anion-exchange chromatography. Its electrophoretic mobility was compared to that of the H1 and H2 heavy chains of I.alpha.I. In reducing conditions, it was quite similar to that of H2 (M(r) 85 000) but clearly different from that of H1 (M(r) 78 000). Thus, the so-determined apparent M(r) of H3 was overestimated since its molecular mass determined by MALDI-TOF was 74 100. This result agrees with the proposed structure for H3. Indeed, by carbohydrate analysis and PNGase F digestion, we demonstrate that the two potential N-glycosylation sites present in the core-protein (theoretical mass: 69 454) are really occupied by two N-glycans, probably of biantennary type.

L59 ANSWER 7 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96239053 EMBASE
DOCUMENT NUMBER: 1996239053
TITLE: Inter-.alpha.-trypsin inhibitor and its related proteins in Syrian hamster urine and plasma.
AUTHOR: Yamamoto T.; Yamamoto K.; Sinohara H.
CORPORATE SOURCE: Department of Biochemistry, Kinki University School of Medicine,Osaka-Sayama, Osaka 589, Japan
SOURCE: Journal of Biochemistry, (1996) 120/1 (145-152).
ISSN: 0021-924X CODEN: JOBIAO

COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Urinary excretion of trypsin inhibitor increased after injection of a carcinogen, N-nitrosobis(2-oxopropyl)amine, into Syrian hamsters. Two inhibitors were purified to apparent homogeneity from urine collected during the course of the carcinogenesis experiment. Their complete amino acid sequences were determined by Edman degradation of the intact proteins and partially degraded fragments. One corresponded to a hamster liver cDNA clone that hybridized with human **bikunin** probe, except that the protein sequence lacked C-terminal serine and the other was trypstatin, the C-terminal half of the **bikunin** molecule. Three proteins containing covalently linked **bikunin** were also identified in pooled blood plasma. They were all dissociated into heavy and light chains by treatment with chondroitinase ABC or 50 mM NaOH, but not by heating at 100.degree.C in the presence of **sodium** dodecyl sulfate and dithiothreitol. N-terminal amino acid sequence analyses of the native chains and partially degraded fragments thereof revealed that these proteins are (i) human-type inter-.alpha.-trypsin inhibitor, consisting of heavy chains 1 and 2 and **bikunin**, (ii) bovine-type inter-.alpha.-trypsin inhibitor, consisting of heavy chains 2 and 3 and **bikunin**, and (iii) pre-.alpha.-trypsin inhibitor, consisting of heavy chain 3 and **bikunin**. Heterodimer of **bikunin** /heavy chain 1 or **bikunin**/heavy chain 2 was not detected. These results suggest that the composition, and hence function, of the inter-.alpha.-trypsin inhibitor family differs considerably from species to species.

L59 ANSWER 8 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93118658 EMBASE
DOCUMENT NUMBER: 1993118658
TITLE: Presence of the protein-glycosaminoglycan-protein covalent cross-link in the inter-.alpha.-inhibitor-related proteinase inhibitor heavy chain 2/**bikunin**.
AUTHOR: Enghild J.J.; Salvesen G.; Thogersen I.B.; Valnickova Z.; Pizzo S.V.; Hefta S.A.
CORPORATE SOURCE: Dept. of Pathology, Duke University Medical Ctr., P.O. Box 3712,Durham, NC 27710, United States
SOURCE: Journal of Biological Chemistry, (1993) 268/12 (8711-8716). ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB HC2/**bikunin** is a human plasma proteinase inhibitor composed of two polypeptide chains that resist dissociation under reducing conditions in SDS- polyacrylamide gel electrophoresis. This observation suggests that a nondisulfide cross-link is responsible for the association of these two polypeptide chains. In this study, we have utilized a variety of techniques to investigate the structural basis for this observation. We show that the cross-link between the two protein chains is sensitive to chondroitin sulfate-degrading enzymes and to 50 mM NaOH, properties shared by the protein-glycosaminoglycan-protein cross-link found in the related pre-.alpha.- inhibitor (Enghild, J. J., Salvesen, G., Hefta, S., Thogersen, I. B., Rutherfurd, S., and Pizzo, S. V. (1991) J. Biol. Chem. 266, 747-751). Biochemical and mass spectrometric analysis of the peptides containing the cross-link indicate that it is mediated by a chondroitin-4-sulfate chain that originates from a typical O-glycosidic link to Ser10 of **bikunin**. The COOH- terminal Asp648 residue of heavy chain 2 is esterified via the .alpha.-carbon to C-6 of an internal N-acetylgalactosamine of the chondroitin-4-sulfate chain. This suggests that the protein-glycosaminoglycan-protein cross-link that assembles the chains of pre-.alpha.-inhibitor is identical to that which assembles HC2/ **bikunin**, and is probably a characteristic of the **bikunin** proteins.

L59 ANSWER 9 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92209773 EMBASE

DOCUMENT NUMBER: 1992209773
TITLE: Biosynthesis of **bikunin** (urinary trypsin inhibitor) in rat hepatocytes.
AUTHOR: Sjoberg E.M.; Fries E.
CORPORATE SOURCE: Med./Physiological Chemistry Dept., Biomedical Center, University of Uppsala,S-751 23 Uppsala, Sweden
SOURCE: Archives of Biochemistry and Biophysics, (1992) 295/2 (217-222).
ISSN: 0003-9861 CODEN: ABBIA4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB One of the major sulfated proteins secreted by rat hepatocytes contains a low-sulfated chondroitin sulfate chain and its apparent molecular mass upon **sodium** dodecyl sulfate/polyacrylamide gel electrophoresis shifts from 40 to 28 kDa upon chondroitinase ABC treatment (E. M. Sjoberg and E. Fries, 1990, Biochem. J. 272, 113-118). These properties suggest that this protein is the rat homologue of the major trypsin inhibitor of human urine which was recently named **bikunin**. In serum, **bikunin** occurs mainly as a subunit of the pre-.alpha.-inhibitor and the inter-.alpha.-inhibitor; in these proteins it is covalently linked to the other polypeptides through its chondroitin sulfate chain. **Bikunin** has been shown to be synthesized by liver cells as a 42-kDa precursor, in which it is linked to .alpha.1-microglobulin by two basic amino acids. We have isolated **bikunin** from rat urine and prepared antibodies against it. In rat hepatocytes pulse-labeled with [35S]methionine, these antibodies precipitated a labeled protein of 42 kDa. Upon chase, three different labeled proteins were recognized by the antibodies in the medium: one protein of 40 kDa (free **bikunin**), one of 125 kDa (presumably pre-.alpha.- inhibitor), and one >240 kDa (possibly a protein related to the inter-.alpha.- inhibitor). Pulse-chase experiments with [35S]sulfate showed that these proteins occurred intracellularly as precursors containing .alpha.1- microglobulin. These results demonstrate that the completion of the chondroitin sulfate chain and its coupling to other polypeptide chains occur before the cleavage of the .alpha.1-microglobulin/**bikunin** precursor.

```
=> s aprotinin and clearance
TOTAL FOR ALL FILES
L66        353 APROTININ AND CLEARANCE

=> s aprotinin and mucociliary clearance
TOTAL FOR ALL FILES
L73          8 APROTININ AND MUCOCILIARY CLEARANCE

=> s l73 not 2000-2002/py
TOTAL FOR ALL FILES
L80          2 L73 NOT 2000-2002/PY

=> dup rem
ENTER L# LIST OR (END):180
PROCESSING COMPLETED FOR L80
L81          2 DUP REM L80 (0 DUPLICATES REMOVED)

=> d ibib abs

L81  ANSWER 1 OF 2     MEDLINE
ACCESSION NUMBER:    92108915     MEDLINE
DOCUMENT NUMBER:     92108915   PubMed ID: 1722377
TITLE:               Tissue kallikrein stimulates mucociliary activity in the
                     rabbit maxillary sinus.
AUTHOR:              Lindberg S; Olsson H
CORPORATE SOURCE:    Department of Oto-Rhino-Laryngology, University Hospital,
                     Lund, Sweden.
SOURCE:              ACTA OTO-LARYNGOLOGICA, (1991) 111 (6) 1126-32.
                     Journal code: 0370354. ISSN: 0001-6489.
```

PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920302
Last Updated on STN: 20000303
Entered Medline: 19920213

AB The in vivo effect of tissue kallikrein on the mucociliary activity in the rabbit maxillary sinus was investigated administering the substance (0.1-5 mU/kg) via a. maxillaris and recording the response with a non-invasive photoelectric technique. Tissue kallikrein accelerated mucociliary activity, with a maximum response for the dose 5 mU/kg (33.7 +/- 13.4% from basal levels, n = 5). The effect had a latency of abut 1 min, with a peak within 2-3 min after the beginning of the administration. The response to tissue kallikrein displayed tachyphylaxis with a second dose producing a weaker response. Pretreatment with the protease inhibitor **aprotinin** (10,000 KIU bolus/kg) inhibited the action of tissue kallikrein. Tissue kallikrein probably stimulates mucociliary activity by producing lysylbradykinin from kininogen. Bradykinin has in an earlier study been shown to stimulate mucociliary activity.

=> d ibib abs 2

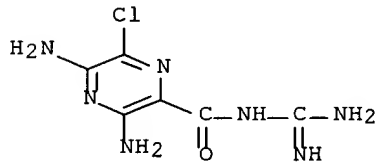
L81 ANSWER 2 OF 2 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92037735 EMBASE
DOCUMENT NUMBER: 1992037735
TITLE: Mucosal penetration enhancers for facilitation of peptide and protein drug absorption.
AUTHOR: Lee V.H.L.; Yamamoto A.; Kompella U.B.
CORPORATE SOURCE: University of Southern California, School of Pharmacy, Department of Pharmaceutical Sciences, 1985 Zonal Avenue, Los Angeles, CA 90033, United States
SOURCE: Critical Reviews in Therapeutic Drug Carrier Systems, (1991) 8/2 (91-192).
ISSN: 0743-4863 CODEN: CRTSEO
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

=> log y

```
=> file reg
=> s amiloride/cn
L1            1 AMILORIDE/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   2609-46-3  REGISTRY
CN   Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
CN   Pyrazinecarboxamide, N-amidino-3,5-diamino-6-chloro- (7CI, 8CI)
OTHER NAMES:
CN   (3,5-Diamino-6-chloropyrazinoyl)guanidine
CN   Amiloride
CN   Amipramidin
CN   Guanamprazine
CN   MK 870
CN   N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide
FS   3D CONCORD
DR   137053-85-1
MF   C6 H8 Cl N7 O
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,
       CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, IFICDB,
       IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, SPECINFO,
       TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)
```




```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

          1911 REFERENCES IN FILE CA (1962 TO DATE)
           109 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
          1911 REFERENCES IN FILE CAPLUS (1962 TO DATE)
             1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> file caplus
=> s l1
L2        1913 L1

=> s l2 and (serine protease or serine proteinase or elastase)
L3          12 L2 AND (SERINE PROTEASE OR SERINE PROTEINASE OR ELASTASE)

=> d 1-12 ibib abs

L3   ANSWER 1 OF 12  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:90621  CAPLUS
DOCUMENT NUMBER:          136:145280
TITLE:                    Treatment of diseases of the eye characterized by the
                          formation of metalloproteinase
INVENTOR(S):              Berman, Charles L.
PATENT ASSIGNEE(S):       USA
```

SOURCE: U.S. Pat. Appl. Publ., 11 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002013345	A1	20020131	US 1998-169660	19981009
US 6384081	B2	20020507		

AB The instant invention provides a method of inhibiting the formation of metalloproteinase and its species, within the eyes of a patient inflicted with at least one form of retinitis characterized by the presence of metalloproteinase, through the administration of an effective dosage that includes an a tetracycline analog, its salts, conjugates or derivs. In an alternate preferred embodiment of the invention the dosage includes at least one other therapeutic substance in effective combination with a tetracycline analog.

L3 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:508083 CAPLUS
DOCUMENT NUMBER: 135:238438
TITLE: Species Specificity of Amidine-Based Urokinase Inhibitors
AUTHOR(S): Klinghofer, Vered; Stewart, Kent; McGonigal, Tom; Smith, Richard; Sarthy, Aparna; Nienaber, Vicki; Butler, Chris; Dorwin, Sarah; Richardson, Paul; Weitzberg, Moshe; Wendt, Mike; Rockway, Todd; Zhao, Xumiao; Hulkower, Keren I.; Giranda, Vincent L.
CORPORATE SOURCE: Departments of Cancer Research and Advanced Technology, Abbott Laboratories, Abbott Park, IL, 60064-6117, USA
SOURCE: Biochemistry (2001), 40(31), 9125-9131
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inhibition of the proteolytic activity of urokinase has been shown to inhibit the progression of tumors in rodent models and is being investigated for use in human disease. Understanding the rodent/human species-specificity of urokinase inhibitors is therefore crit. for interpretation of rodent cancer progression models that use these inhibitors. We report here studies with a panel of 11 diverse urokinase inhibitors in both human and mouse enzymic assays. Inhibitors such as amiloride, B428, and naphthamidine, that occupy only the S1 subsite pocket were found to be nearly equipotent between the human and the murine enzymes. Inhibitors that access addnl., more distal, pockets were significantly more potent against the human enzyme but there was no corresponding potency increase against the murine enzyme. X-ray crystallog. structures of these compds. bound to the **serine protease** domain of human urokinase were solved and examd. in order to explain the human/mouse potency differences. The differences in inhibitor potency could be attributed to four amino acid residues that differ between murine and human urokinases: 60, 99, 146, and 192. These residues are Asp, His, Ser, and Gln in human and Gln, Tyr, Glu, and Lys in mouse, resp. Compds. bearing a cationic group that interacts with residue 60 will preferentially bind to the human enzyme because of favorable electrostatic interactions. The hydrogen bonding to residue 192 and steric considerations with residues 99 and 146 also contribute to the species specificity. The nonparallel human/mouse enzyme inhibition observations were extended to a cell-culture assay of urokinase-activated plasminogen-mediated fibronectin degrdn. with analogous results. These studies will aid the interpretation of in vivo evaluation of urokinase inhibitors.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:506288 CAPLUS
DOCUMENT NUMBER: 135:298725

TITLE: Na+ transport in normal and CF human bronchial epithelial cells is inhibited by BAY 39-9437
AUTHOR(S): Bridges, Robert J.; Newton, Ben B.; Pilewski, Joseph M.; Devor, Daniel C.; Poll, Christopher T.; Hall, Rod L.
CORPORATE SOURCE: Department of Cell Biology and Physiology, University of Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: American Journal of Physiology (2001), 281(1, Pt. 1), L16-L23
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To test the hypothesis that Na+ transport in human bronchial epithelial (HBE) cells is regulated by a protease-mediated mechanism, we investigated the effects of BAY 39-9437, a recombinant Kunitz-type **serine protease** inhibitor, on amiloride-sensitive short-circuit current of normal [non-cystic fibrosis (CF) cells] and CF HBE cells. Mucosal treatment of non-CF and CF HBE cells with BAY 39-9437 decreased the short-circuit current, with a half-life of .apprx.45 min. At 90 min, BAY 39-9437 (470 nM) reduced Na+ transport by .apprx.70%. The inhibitor effect of BAY 39-9437 was concn. dependent, with a half-maximal inhibitory concn. of .apprx.25 nM. Na+ transport was restored to control levels, with a half-life of .apprx.15 min, on washout of BAY 39-9437. In addn., trypsin (1 .mu.M) rapidly reversed the inhibitory effect of BAY 39-9437. These data indicate that Na+ transport in HBE cells is activated by a BAY 39-9437-inhibitable, endogenously expressed **serine protease**. BAY 39-9437 inhibition of this **serine protease** maybe of therapeutic potential for the treatment of Na+ hyperabsorption in CF.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:534024 CAPLUS
DOCUMENT NUMBER: 133:276293
TITLE: Crystals of the Urokinase Type Plasminogen Activator Variant .beta.c-uPA in Complex with Small Molecule Inhibitors Open the Way towards Structure-based Drug Design
AUTHOR(S): Zeslawska, Ewa; Schweinitz, Andrea; Karcher, Annette; Sondermann, Peter; Sperl, Stefan; Sturzebecher, Jorg; Jacob, Uwe
CORPORATE SOURCE: Abteilung Strukturforschung, Max-Planck-Institut fur Biochemie, Martinsried, D-82152, Germany
SOURCE: Journal of Molecular Biology (2000), 301(2), 465-475
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Urokinase is a **serine protease** involved in cancer growth and metastasis. Here the authors present the first urokinase crystal structure in complex with reversible inhibitors at 2.1 and 2.6 .ANG. resoln. These inhibitor complex structures have been obtained from crystals of engineered urokinase type plasminogen activator designed to obtain a crystal form open for inhibitor soaking. The mutant C122S loses its flexible A-chain upon activation cleavage and crystallizes in the presence of benzamidine, which was later displaced by the desired inhibitor. This new soakable crystal form turned out to be of great value in the process of structure-based drug design. The evaluated binding mode of amiloride, and UKI-1D revealed a new subsite of the primary specificity pocket of urokinase that will be employed in the future ligand optimization process. (c) 2000 Academic Press.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:441647 CAPLUS
DOCUMENT NUMBER: 133:84295
TITLE: Kunitz-type **serine proteinase** inhibitors for accelerating the rate of mucociliary

clearance
INVENTOR(S): Hall, Roderick; Poll, Christopher T.; Newton, Benjamin B.; Taylor, William J. A.
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037099	A2	20000629	WO 1999-GB4381	19991222
WO 2000037099	A3	20001026		
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1140150	A2	20011010	EP 1999-963636	19991222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002532558	T2	20021002	JP 2000-589209	19991222

PRIORITY APPLN. INFO.: US 1998-218913 A 19981222
US 1999-441966 A 19991117
WO 1999-GB4381 W 19991222

AB The instant invention provides for a compn. and method for using Kunitz-type **serine protease** inhibitors, e.g., aprotinin or bikunin, for stimulating the rate of mucociliary clearance of mucus and sputum in lung airways of subjects afflicted with mucociliary dysfunctions such as cystic fibrosis.

L3 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:669261 CAPLUS
DOCUMENT NUMBER: 132:160893
TITLE: Molecular basis of specific inhibition of urokinase plasminogen activator by amiloride
AUTHOR(S): Jankun, Jerzy; Skrzypczak-Jankun, Ewa
CORPORATE SOURCE: Urology Research Center, Department of Urology, Medical College of Ohio, Toledo, OH, USA
SOURCE: Cancer Biochemistry Biophysics (1999), 17(1-2), 109-123
CODEN: CABCD4; ISSN: 0305-7232
PUBLISHER: Gordon & Breach Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) are very similar **serine proteases** with the same physiol. function, the activation of plasminogen. An increased amt. or activity of uPA but not tPA has been detected in human cancers. The PAs are weak proteolytic enzymes, but they activate plasminogen to plasmin, a strong proteolytic enzyme largely responsible for the malignant properties of cancers. It has been shown recently that the administration of uPA inhibitors can reduce tumor size. Inhibitors of uPA could therefore be used as anti-cancer and anti-angiogenesis agents. It has been found that amiloride competitively inhibits the catalytic activity of uPA but not tPA. Modification of this chem. could therefore produce a new class of uPA specific inhibitors and a new class of anti-cancer agents. The X-ray structure of the uPA complex with amiloride is not known. There are structural differences in the specificity pocket of uPA and tPA. However, the potential energy of binding amiloride is lower outside this cavity in the case of tPA. A region responsible for binding amiloride to tPA has been proposed as the loop B93-B101, reached in neg. charged amino acids present in tPA but not uPA.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:548471 CAPLUS
DOCUMENT NUMBER: 131:314149
TITLE: Organic cation transport in rabbit alveolar epithelial cell monolayers
AUTHOR(S): Shen, Jie; Elbert, Katharina J.; Yamashita, Fumiyoshi; Lehr, Claus-Michael; Kim, Kwang-Jin; Lee, Vincent H. L.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Southern California, Los Angeles, CA, 90033, USA
SOURCE: Pharmaceutical Research (1999), 16(8), 1280-1287
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Org. cation (OC) transport in primary cultured rabbit alveolar epithelial cell monolayers was characterized using [14C]-guanidine as a model substrate. Type II alveolar epithelial cells from the rabbit lung were isolated by **elastase** digestion and cultured on permeable filters precoated with fibronectin and collagen. Uptake and transport studies of [14C]-guanidine were conducted in cell monolayers of 5 to 6 days in culture. The cultured alveolar epithelial cell monolayers exhibited the characteristics of a tight barrier. [14C]-Guanidine uptake was temp. dependent, saturable, and inhibited by OC compds. such as amiloride, cimetidine, clonidine, procainamide, propranolol, tetraethylammonium, and verapamil. Apical guanidine uptake (Km = 129 .+-. 41 .mu.M, Vmax = 718 .+-. 72 pmol/mg protein/5 min) was kinetically different from basolateral uptake (Km = 580 .+-. 125 .mu.M, Vmax = 1,600 .+-. 160 pmol/mg protein/5 min). [14C]-Guanidine transport across the alveolar epithelial cell monolayer in the apical to basolateral direction revealed a permeability coeff. (Papp) of (7.3 .+-. 0.4) .times. 10-7 cm/s, about seven times higher than that for the paracellular marker [14C]-mannitol. Our findings are consistent with the existence of carrier-mediated OC transport in cultured rabbit alveolar epithelial cells.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:85185 CAPLUS
DOCUMENT NUMBER: 128:228162
TITLE: CASP2 molecular docking predictions with the LIGIN software
AUTHOR(S): Sobolev, Vladimir; Moallem, Theodore M.; Wade, Rebecca C.; Vriend, Gert; Edelman, Marvin
CORPORATE SOURCE: Department of Plant Genetics, Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Proteins: Structure, Function, and Genetics (1998), Volume Date 1997, (Suppl. 1), 210-214
CODEN: PSFGEY; ISSN: 0887-3585
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Seven docking predictions were made with the LIGIN program. In six cases the location of the binding pocket was identified correctly by systematically docking everywhere within the protein structure. In two cases the ligand was docked to within 1.8 .ANG. RMSD of the exptl. detd. structure. LIGIN has not been optimized to deal with highly flexible ligands that dock at the surface of proteins. Consequently, in three cases the exposed part of the ligand was docked poorly, although the buried parts were docked well, and made similar at. contacts with the protein as in the exptl. detd. structure.

L3 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:742510 CAPLUS
DOCUMENT NUMBER: 128:57249
TITLE: Competitive inhibition of swine kidney copper amine oxidase by drugs: amiloride, clonidine, and gabexate mesylate
AUTHOR(S): Federico, Rodolfo; Angelini, Riccardo; Ercolini, Luca; Venturini, Giorgio; Mattevi, Andrea; Ascenzi, Paolo

CORPORATE SOURCE: Department of Biology, Third University of Rome, Rome, 00146, Italy
SOURCE: Biochemical and Biophysical Research Communications (1997), 240(1), 150-152
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Competitive inhibition of swine kidney copper amine oxidase by diuretic, antihypertensive, and anticoagulant drugs, amiloride, clonidine, and gabexate mesylate, resp., is reported. The affinity of these compds. for swine kidney copper amine oxidase is similar to that obsd. for inhibitor binding to nitric oxide synthase and trypsin-like **serine proteinases**. This finding suggests that amiloride, clonidine, and gabexate mesylate should be administrated under careful control, since enzyme cross-inhibition may occur also in vivo.

L3 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:440959 CAPLUS
DOCUMENT NUMBER: 119:40959
TITLE: Enzyme inhibitors for treatment of periodontosis
INVENTOR(S): Imaizumi, Kazuo
PATENT ASSIGNEE(S): Lion Corp, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05097708	A2	19930420	JP 1991-282090	19911002

AB ATPase inhibitors, cysteine or **serine protease** inhibitors, and/or protein kinase C inhibitors are useful for treatment of periodontosis. Acetazolamide inhibited Ca release from bone by Porphyromonas gingivalis lipopolysaccharide at ED50 of 10-4M. Acetazolamide 1, PVP 65, poly(acrylic acid) Na salt 20, PEG 10, and H2O to 100% were mixed to give a compn.

L3 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:182795 CAPLUS
DOCUMENT NUMBER: 118:182795
TITLE: Bis(5-amidino-2-benzimidazolyl)methane and related amidines are potent, reversible inhibitors of mast cell tryptases
AUTHOR(S): Caughey, G. H.; Raymond, W. W.; Bacci, E.; Lombardy, R. J.; Tidwell, R. R.
CORPORATE SOURCE: Cardiovasc. Res. Inst., Univ. California, San Francisco, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 264(2), 676-82
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tryptase is the major secretory protease of human mast cells and is proposed to be involved in neuropeptide processing and tissue inflammation. Exploration of the biol. of tryptase has been hindered by the lack of potent, selective inhibitors. The current study explores the properties of arom. diamidines as inhibitors of dog and human tryptase. The strongest inhibitors of tryptase in this series are bis(5-amino-2-benzimidazolyl)methane (BABIM) and (5-amidino-2-benzimidazolyl)-(5-N,N'-dimethylamidino)-2-benzimidazolyl)methane, which exhibit Ki values of 1.8 and 1.4 nM, resp., in blocking the hydrolysis of tosyl-L-Gly-Pro-Lys-4-nitroanilide by human tryptase. These compds. are .apprx.10,000-fold more potent than benzamidine, and are the strongest reversible inhibitors of tryptase described to date. Other arom. mono- and diamidines, including amiloride and pentamidine, are less potent. Nonetheless, they abolish tryptase activity at high inhibitor concns. The rank order of tryptase inhibitor potency parallels that of inhibitors tested against trypsin. BABIM, the only highly active member of this

series whose potency against other targets has been examd. previously, is a far stronger inhibitor of tryptase than of other trypsin-like **serine proteases**, including those involved with hemostasis, fibrinolysis and the complement system. Therefore, BABIM appears to have selective affinity for tryptase. In addn. to inhibiting tryptase-induced hydrolysis of peptide-based chromogenic substrates, BABIM blocks completely the reversal of vasoactive intestinal peptide-induced relaxation of isolated trachea by dog tryptase. Thus, BABIM and related amidines are potent inhibitors of mast cell tryptases that may be useful in exploring mast cell protease biol.

L3 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1982:48256 CAPLUS
DOCUMENT NUMBER: 96:48256
TITLE: Kallikrein inhibitors decrease short-circuit current by inhibiting sodium uptake
AUTHOR(S): Orce, Gabriel G.; Castillo, Graciela A.; Margolius, Harry S.
CORPORATE SOURCE: Dep. Pharmacol., Med. Univ. South Carolina, Charleston, SC, 29425, USA
SOURCE: Hypertension (1981), 3(6, Pt. 2), 92-5
CODEN: HPRTDN; ISSN: 0194-911X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB aprotinin [9087-70-1], A reversible inhibitor, and D-Phe-Phe-Arg chloromethyl ketone (DPPA) [74392-49-7], an irreversible inhibitor of kallikrein [9001-01-8] decreases short-circuit current (SCC) in the urinary bladder of the toad Bufo marinus in a dose-dependent fashion. Both agents act more rapidly and potently when added to the mucosal side of the bladder, exhibiting similar potency and effectiveness. To further define their sites of action, amphotericin B [1397-89-3] was used ; this interacts with the mucosal cell membrane and increases its cation permeability, presumably by altering a barrier at the apical border that limits the rate of Na+ uptake by epithelial cells. Thus, the SCC-inhibiting effects of amiloride [**2609-46-3**] were reversed by mucosal amphotericin B treatment. The effects of either aprotinin or DPPA were reversed after the addn. of amphotericin B (2.0 .times. 10-5 M) to the mucosal side of the bladder. Also, when initial SCC was completely blocked by amiloride (1.0 .times. 10-4M), the addn. of amphotericin B (2.0 .times. 10-5 M) to the mucosal bath induced an amiloride-insensitive SCC, which was not affected by high concns. of either aprotinin or DPPA, but was inhibited by serosal addn. of ouabain (1.0 .times. 10-5 M). Thus, these kallikrein inhibitors act at a site along the active transport pathway that is proximal to the ouabain-sensitive site, and removal of the apical barrier by amphotericin B prevents their effect on SCC. The apical barrier appears to be a likely site of the action of these agents on SCC, suggesting a close relation between this structure and a **serine proteinase** involved in the uptake of Na+ by the toad bladder.

=> log y